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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	10

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/606,222	Applicant(s) THOMAS ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *18 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,19-34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-37 are pending.

Claims 1-17, 19-35 and 37 are under current examination.

Any rejection made of record in the prior Office action, mailed 6/20/01, Paper No. 6,and not made of record in the instant Office action, has been withdrawn in view of Applicants amendments to the claims.

Response to Arguments

Applicant's arguments filed 12/20/01, Paper No. 8, have been fully considered` but they are not persuasive.

Election/Restrictions

Applicants' affirmation of the election of the invention of Group I is noted. It is noted that the method of the claimed invention is directed to methods of deleting a nucleic acid in specified tissues of an animal, a nucleic acid molecule and a transgenic animal containing the nucleic acid molecule (see p. 4, 1st paragraph of Response).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1-17, 9-35 and 37 under 35 U.S.C. 112, first paragraph, is maintained for reasons advanced on pages 3-8 of the prior Office Action.

The specification, while being enabling for a method for deleting a nucleic acid sequence in a specified tissue of a mouse from a DNA molecule introduced into the mouse, comprising introducing a DNA molecule which comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site, growing the mouse so that the tissue-specific promoter is active for expression of the recombinase gene in the specific tissue, and where the foreign DNA is deleted in the specified tissue during growth of the mouse, the specification does not reasonably provide enablement for a method for deleting a nucleic acid sequence in a specified tissue of organisms, to the breadth claimed, from a DNA introduced into the organism, comprising introducing a DNA molecule which comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site, the growing of organisms, to the breadth claimed, so that the tissue-specific promoter is active for expression of the recombinase gene in the specific tissue, and where the foreign DNA is deleted in the specified tissue during growth of organisms to the breadth claimed. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches in targeted germ-line modification of the mammalian genome and there exists an art-recognized need to improve methods for removing marker genes, as the marker genes often cause differences in transformation and recombination efficiencies (see p. 1, lines 15-30). The specification provides teachings for a method of self-excision of nucleic acid sequences in specific tissues of organisms by use of a DNA molecule comprising a recombinase site, a tissue specific promoter, a recombinase gene, a foreign DNA and a recombinase site; the specification further provides a transgenic organism containing the nucleic acid molecule (see p. 2, lines 24-25).

Applicants argue that embryonic stem (ES) cells are not an essential element of the invention (see p. 5, lines 1-2 of Response). Applicants further argue that the specification provides stem cells as an example of how the claimed invention works with a particular cell type (see p. 5, 2nd paragraph). Further, Applicants argue that the claimed invention is not directed to the *generation* of a transgenic animal, but to the prevention of a transgenic animal producing progeny containing a heterologous DNA (see p. 5, 2nd paragraph, lines 14-18).

In response, it is noted that the claimed invention reads on the deletion of nucleic acid sequences from a DNA molecule that has been introduced into an organism (see, for example, claim 1, lines 1-2), and in further embodiments, the

organism is a transgenic organism (see, for claim 11). As Applicants have stated, the claimed invention is not directed to the generation of a transgenic animal; however, certain embodiments of the present invention require the use of a transgenic animal. As such, it is reiterated that the state of the art of producing transgenic animals is unpredictable, as evidenced by Moreadith *et al.* and Mullins *et al.* (see prior Office action, p. 6-7). A demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. As such, the Examiner maintains that ES cells are elements essential to certain embodiments of the claimed invention.

Furthermore, Applicants argue that the claimed invention is directed to methods for particular cell type, and provide the example of using chimeric mouse having a copy of a DNA molecule of the invention excised from a target gene from the germline (see p. 5, 2nd paragraph). It is reiterated that although the claimed invention is not limited to the use of transgenic animals, certain of the instant claims are directed to transgenic animals, and as such require the use of ES cells (see above).

Applicants further argue that gene therapy is not an essential element of the claimed invention (see p. 5, 1st paragraph of Response). Furthermore, Applicants argue that the invention is not directed to gene therapy (see p. 5, 2nd paragraph, line 7). In response, it is noted that the Examiner has not identified gene therapy

as an essential element, but has directed her arguments to embodiments of the invention that are particularly directed to gene therapy (e.g., claims 32, 33, 34); and in particular, in germline gene therapy. Some of the instant claims state that the promoter of the nucleic acid molecule is specific to the male or female gamete, and the foreign DNA is used in gene therapy (e.g., claim 33). As such, the Examiner has presented the state of the art of germline gene therapy (see p. 7 of the prior Office action), the claimed invention is not limited to any particular organism, the claimed invention encompasses germline gene therapy in humans.

Applicants argue that the claimed invention does not require therapeutic expression of a gene, as the claimed invention simply provides a method whereby the regulation of when and where a DNA fragment is maintained in a cellular chromosomal complement (see p. 5, 2nd paragraph, lines 12-17 of Response), and further provide an example wherein the claimed method is utilized to prevent the transmission of a heterologous gene to the progeny of a transgenic animal. The Examiner maintains that certain embodiments of the claimed invention are directed for use in gene therapy (e.g., claim 6). As such, it is well known that the state of art of gene therapy is undeveloped and unpredictable in achieving *in vivo* therapeutic expression levels of a gene of interest. Although the claimed method is not a method of gene therapy, it requires methods of gene therapy for its implementation, methods that have been shown to be unpredictable and undeveloped.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters listed above for achieving a method for deleting a nucleic acid sequence in the specified tissue of an organism, the lack of direction or guidance provided in the specification for the isolation of animal ES cells from any species, other than that of the mouse, as well as the unpredictable and undeveloped state of the art for the isolation of animal ES cells from species other than mice, as well as the claimed breadth of the claims, encompassing the use of ES cells from any particular organism for the generation of any particular type of organism, the lack of guidance and direction provided by the specification to carry out gene therapy as broadly claimed, involving any particular type of target cell, route of administration and subject, and the unpredictable and undeveloped art of gene therapy, it would have required undue experimentation for one skilled in the art to carry out the claimed methods, nucleic acid constructs, and methods of using the same.

Claim Rejections - 35 USC § 112

The rejection of claims 11, 14, 22-24, 27-34 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicants' Amendment to the claims.

Conclusion

Claims 1-17, 19-35 and 37 appear to be free of the prior art of record, as the prior art of record fails to teach or suggest a method for deleting a nucleic acid sequence in a specified tissue of an animal from a DNA molecule introduced into the animal, where the DNA molecule comprises a recombinase site, a tissue-specific promoter, a recombinase gene, a foreign DNA and a recombinase site, and growing the animal so that the tissue-specific promoter is active for expression of the recombinase gene and the foreign DNA is deleted in the specified tissue during growth of the animal, DNA molecules of the same, and transgenic non-human animals comprising the DNA molecules of the same. However claims 1-17, 19-35 and 37 are subject to other rejections.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory

action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Deborah Crouch

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PRIMARY EXAMINER
GROUP ~~1800~~ 1630

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